

What is claimed is:*Sub a1*

1. A growth factor which activates GFR α 1-RET but does not substantially activate GFR α 2-RET or GFR α 3-RET.

2. The growth factor of claim 1, comprising a chimeric GDNF family ligand or a derivative thereof.

3. The growth factor of claim 2, comprising a persephin having substitutions in regions F2a and F2c wherein the substitutions in region F2a comprise from one to eight amino acids identical to region F2a of GDNF, neurturin or artemin, or conservative amino acid substitutions therefor, and wherein the substitutions in region F2c comprise from one to eight amino acids identical to region F2c of GDNF, neurturin or artemin, or conservative amino acid substitutions therefor.

4. The growth factor of claim 3, wherein the substituted persephin comprises persephin as set forth in SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3 with substitutions in regions F2a and F2c independently selected from corresponding regions of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10.

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5. The growth factor of claim 4, comprising SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:16.

6. The growth factor of claim 4, wherein the substituted persephin comprises a human persephin as set forth in SEQ ID NO:1 with substitutions for amino acid residues 63-66 selected from the group consisting of SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19, and substitutions for amino acid residues 76-82 selected from the group consisting of SEQ ID NO:20, SEQ ID NO:21, and SEQ ID NO:22.

7. The growth factor of claim 6, comprising SEQ ID NO:23, SEQ ID NO:24 or SEQ ID NO:25.

8. The growth factor of claim 6, consisting of SEQ ID NO:26, SEQ ID NO:27 or SEQ ID NO:28.

9. A composition comprising the growth factor of claim 1 in a pharmaceutically acceptable preparation.

10. A nucleic acid comprising a polynucleotide encoding the growth factor of claim

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11. The nucleic acid of claim 10, wherein the encoded growth factor is a chimeric GDNF family ligand or a conservatively substituted derivative thereof.

12. The nucleic acid of claim 11, wherein the encoded growth factor comprises a persephin having substitutions in regions F2a and F2c wherein the substitutions in region F2a comprise from one to eight amino acids identical to region F2a of GDNF, neurturin or artemin, or conservative amino acid substitutions therefor, and wherein the substitutions in region F2c comprise from one to eight amino acids identical to region F2c of GDNF, neurturin or artemin, or conservative amino acid substitutions therefor.

13. The nucleic acid of claim 12, wherein the encoded substituted persephin comprises persephin as set forth in SEQ ID NO:1, SEQ ID NO:2 or SEQ ID NO:3 with substitutions in regions F2a and F2c independently selected from corresponding regions of SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, or SEQ ID NO:10.

14. The nucleic acid of claim 13, wherein the encoded growth factor comprises SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:16.

15. The nucleic acid of claim 13, wherein the encoded growth factor comprises a human persephin as set forth in SEQ ID NO: 1 with substitutions for amino acid residues 63-66 selected from the group consisting of SEQ ID NO:17, SEQ ID NO:18 and SEQ ID NO:19, and substitutions for amino acid residues 76-82 selected from the group consisting of SEQ ID NO:20, SEQ ID NO:21, and SEQ ID NO:22.

16. The nucleic acid of claim 15, wherein the encoded growth factor comprises SEQ ID NO:23, SEQ ID NO:24 or SEQ ID NO:25.

17. The nucleic acid of claim 15, wherein the encoded growth factor consists of SEQ ID NO:26, SEQ ID NO:27 or SEQ ID NO:28.

18. A vector comprising expression regulatory elements operably linked to the polynucleotide of claim 10.

19. A host cell comprising the vector of claim 18.

20. The host cell of claim 19 which is a bacterial cell, a yeast cell, a plant cell, an insect cell or a mammalian cell.

21. A method for providing trophic support to a mammalian cell or for producing differentiation of a mammalian cell or for both, the method comprising treating the cell with an effective amount of the growth factor of claim 1 or a polynucleotide which encodes for expression of the growth factor.

22. The method of claim 21, wherein the treating step further comprises administering to the cell a GFR α 1 polypeptide.

23. The method of claim 21, wherein the cell is in a patient and the treating comprises administering the growth factor to the patient.

24. The method of claim 23, wherein the administering comprises implanting into the patient a cell which expresses the growth factor.

25. The method of claim 24, wherein the cell is a neuronal cell in a patient suffering from peripheral neuropathy, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, diabetes, AIDS, ischemic stroke, acute brain injury, acute spinal cord injury, a nervous system tumor such as neuroblastomas, multiple sclerosis, infection, side effects of chemotherapy, or an enteric disease such as idiopathic constipation or constipation associated with Parkinson's disease, spinal cord injury or use of opiate pain-killers, or the cell is a non-neuronal cell in a patient suffering from small cell lung carcinoma.

26. A method for preventing or treating cellular degeneration or insufficiency in an individual comprising administering to the individual a therapeutically effective amount of the growth factor of claim 1 or a polynucleotide encodes for expression of the growth factor.

27. The method of claim 26 wherein the administering comprises implanting into the individual a cell which expresses the growth factor.

28. The method of claim 25 wherein the individual suffers from (a) neuronal degeneration resulting from peripheral neuropathy, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, diabetes, AIDS, ischemic stroke, acute brain injury, acute spinal chord injury, a nervous system tumor such as neuroblastomas, multiple sclerosis, infection, side effects of chemotherapy, or an enteric disease such as idiopathic constipation or constipation associated with Parkinson's disease, spinal cord injury or use of opiate pain-killers, (b) from small cell lung carcinoma, (c) from hematopoietic cell degeneration or insufficiency resulting from eosinopenia, basopenia, lymphopenia, monocytopenia, neutropenia, anemias, thrombocytopenia, or stem-cell insufficiencies therefor, or (d) cardiac muscle degeneration or insufficiency resulting from cardiomyopathy or congestive heart failure.

29. A growth factor which activates GFR α 1-RET and GFR α 2-RET but does not substantially activate GFR α 3-RET comprising a persephin having substitutions in regions Ha, F2a and F2c wherein:

(a) the substitutions in region Ha comprise from one to nine amino acids identical to region Ha of neurturin, or conservative amino acid substitutions therefor;

(b) the substitutions in region F2a comprise from one to eight amino acids identical to region F2a of neurturin, or conservative amino acid substitutions therefor; and

(c) the substitutions in region F2c comprise from one to eight amino acids identical to region F2c of neurturin.

30. A nucleic acid comprising a polynucleotide encoding the growth factor of claim 29.

31. A method for providing trophic support to a mammalian cell or for producing differentiation of a mammalian cell or for both, the method comprising treating the cell with

an effective amount of the growth factor of claim 29 or a polynucleotide which encodes for expression of the growth factor.

32. A method for preventing or treating cellular degeneration or insufficiency in an individual comprising administering to the individual a therapeutically effective amount of the growth factor of claim 29 or a polynucleotide which encodes for expression of the growth factor.

33. A growth factor which activates $GFR\alpha 1$ -RET and $GFR\alpha 3$ -RET but does not substantially activate $GFR\alpha 2$ -RET comprising a persephin having substitutions in regions Ha, F2a and F2c wherein:

- 5 (a) the substitutions in region Ha comprise from one to nine amino acids identical to region Ha of artemin, or conservative amino acid substitutions therefor;
- (b) the substitutions in region F2a comprise from one to eight amino acids identical to region F2a of artemin, or conservative amino acid substitutions therefor; and
- (c) the substitutions in region F2c comprise from one to eight amino acids identical to region F2c of artemin.

34. A nucleic acid comprising a polynucleotide encoding the growth factor of claim 33.

35. A method for providing trophic support to a mammalian cell or for producing differentiation of a mammalian cell or for both, the method comprising treating the cell with an effective amount of the growth factor of claim 33 or a polynucleotide which encodes for expression of the growth factor.

36. A method for preventing or treating cellular degeneration or insufficiency in an individual comprising administering to the individual a therapeutically effective amount of the growth factor of claim 33 or a polynucleotide which encodes for expression of the growth factor.